A chemical basis for selective recognition of nonpeptide antigens by human δ T cells[1]

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SPECIFIC AIMS

Human γδ T lymphocytes activate their immune function upon TCR-mediated recognition of antigens not associated with MHC molecules. Because different nonpeptide phosphorylated antigens (phosphoantigens) are selectively recognized by γδ T cells, we clarified its molecular basis through the structure–function relationship of novel synthetic phosphoantigens.

[1] A study dedicated to the memory of Claude de Préval.
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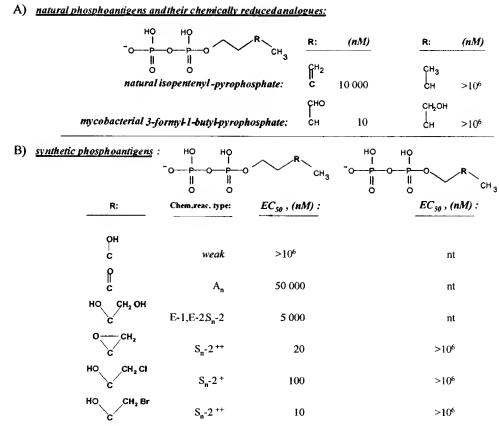

Figure 1. Phosphoantigen structures and specific bioactivities for γδ cells

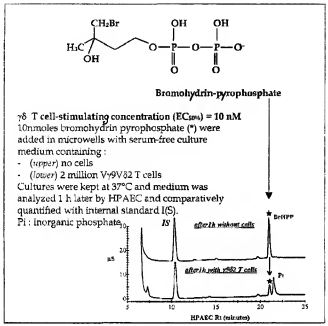

Figure 2. Phosphoantigen degradation by reactive γδ cells

PRINCIPAL FINDINGS

Paradoxically, human γδ T cell-mediated recognition of phosphoantigens is highly specific and broadly cross-reactive. The relationship between structure and activity of several natural or synthetic phosphoantigens shows the importance of conformational determinants, but also reveals the critical role of the chemical reactivity of phosphoantigens. Phosphoepoxides and phosphohalohydrins are new synthetic phosphoantigens that were designed on this basis and constitute the most potent γδ cell-stimulating compounds so far. For optimal Vγ9Vδ2 T cell activation, both organic and phosphorylated moieties of these ligands undergo rapid and degradative chemical changes such as dephosphorylation. This irreversible phosphoantigen consumption is rapid, cell-mediated, and may only be evidenced with compounds bioactive in the nanomolar but not micromolar range. Furthermore, whereas the structure of phosphoantigens is changed upon their recognition by γδ T cells, conversely, chemically resistant phosphoantigen analogs antagonize phosphoantigen-mediated γδ T cell activation.

CONCLUSIONS AND SIGNIFICANCE

These observations reveal a novel mode of antigenic recognition by T cells, associating topological fit with chemical degradation of the phosphoantigens. This explains why phosphoantigens cannot be stably pulsed on presenting cells for recognition and how highly selective but cross-reactive recognition of nonpeptide ligands may occur simultaneously.

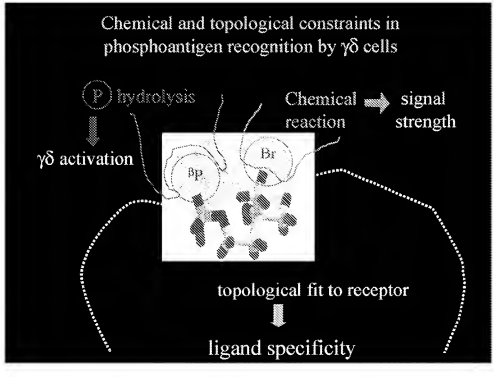

Figure 3. Molecular molecule for the chemical basis of phosphoantigen recognition